OGD/ORS/DQMM
Quantitative Methods and Modeling for Generics

Liang Zhao, Ph.D.
Director, Division of Quantitative Methods and Modeling
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA

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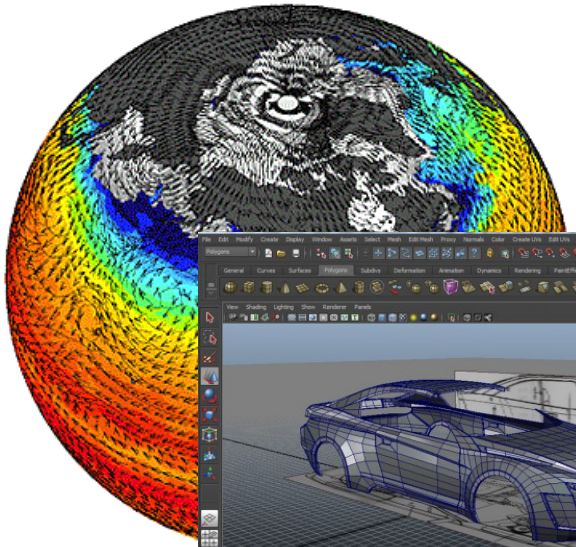
Part 15 Public Meeting, June 5th, 2015

Modeling and Simulation in Other Disciplines

Global Climate



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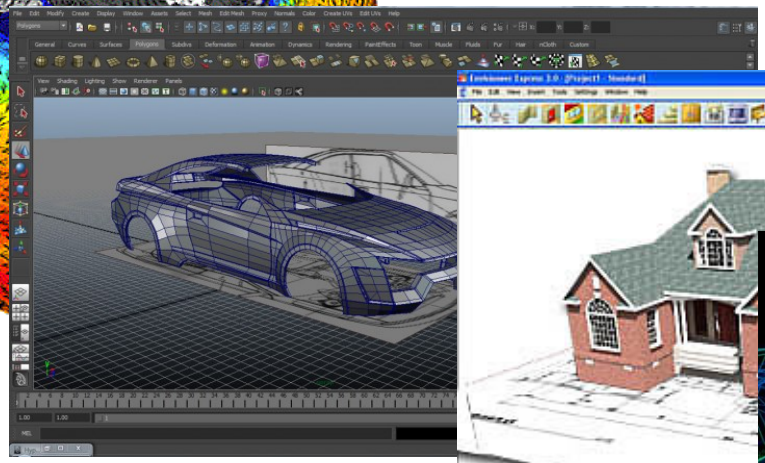
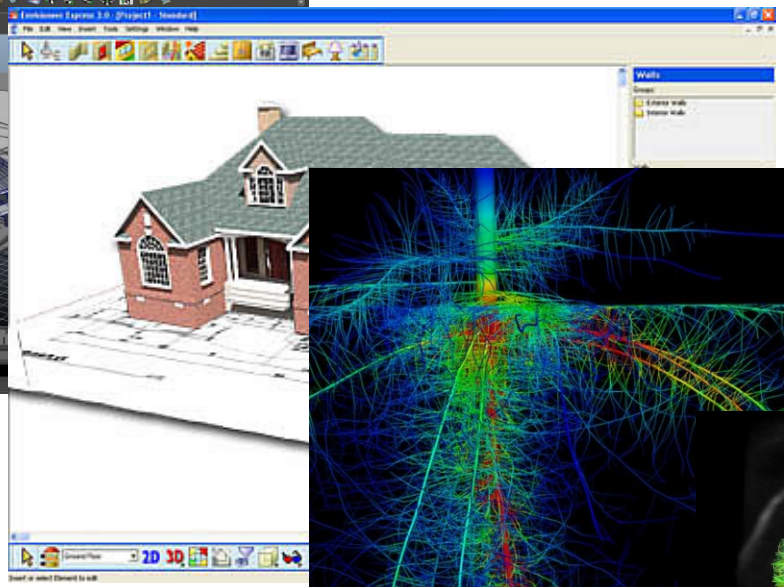
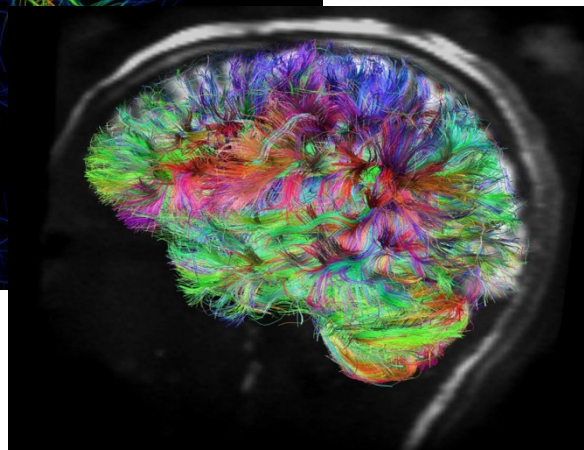


House



Plant

Physiology



Quantitative Approaches for Generics

Industry

- Limited inclusion in ANDAs
- Conventionally used in
  - Model based product design
  - BE study design and assessment

Regulatory

- Complex products, e.g., Copaxone
- Locally acting products: topical, nasal, inhalation, ocular, and GI
- NTI
- Long acting injectable products
- Drugs with steep exposure-response relationships
- In vitro BE assessment
- Safety surveillance
- Others

Modeling & Simulation for Generics

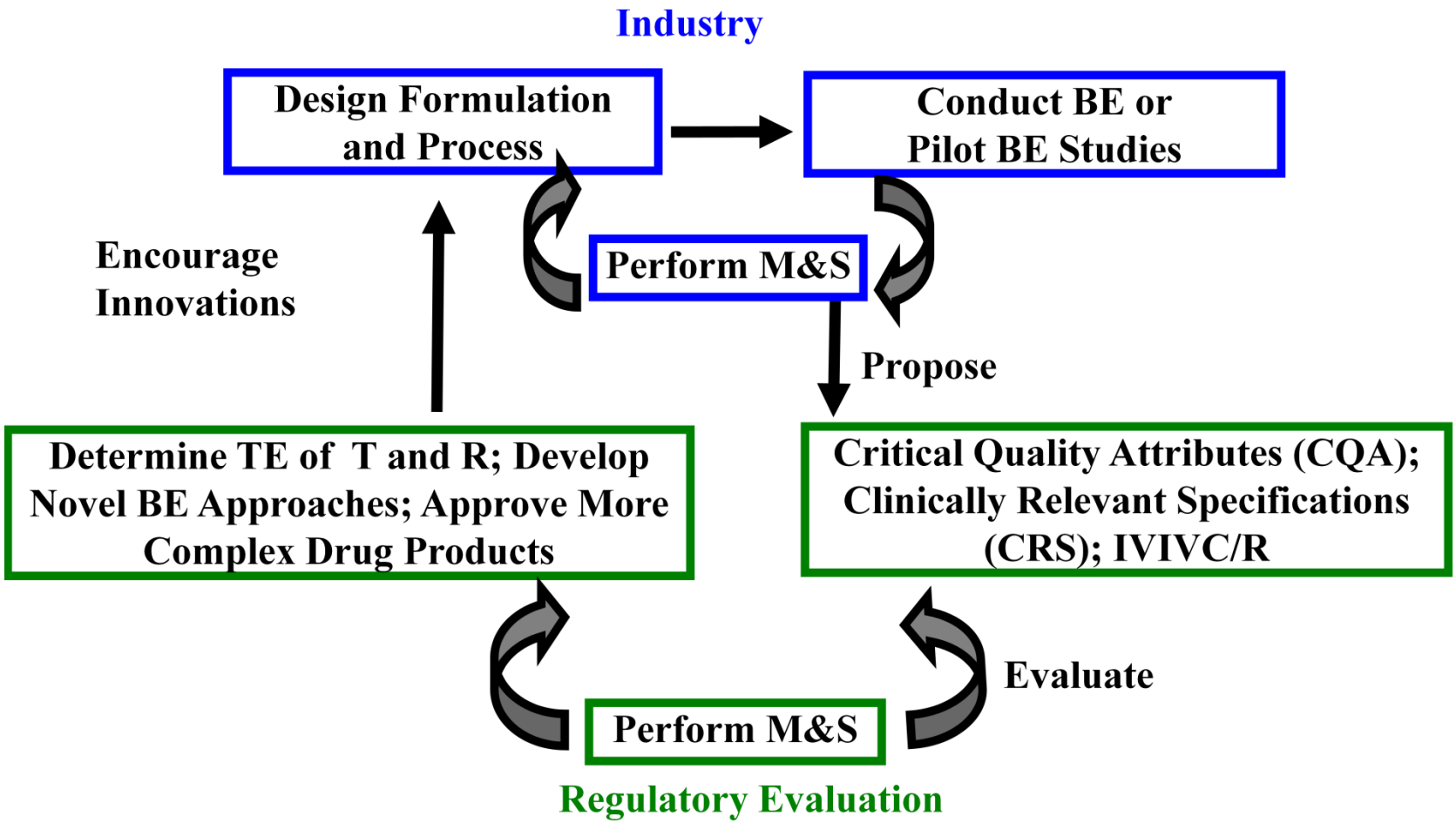


Diagram by Dr. Robert Lionberger

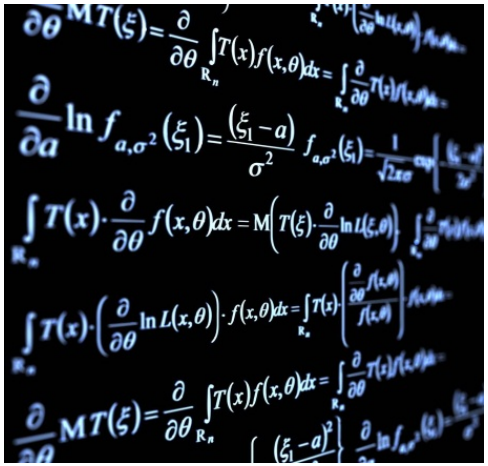
Core DQMM Tool Set

Non-Oral Drug

Oral Drug

Our Goal is to support

- Generic drug research
- Policy development
- Regulatory decisions

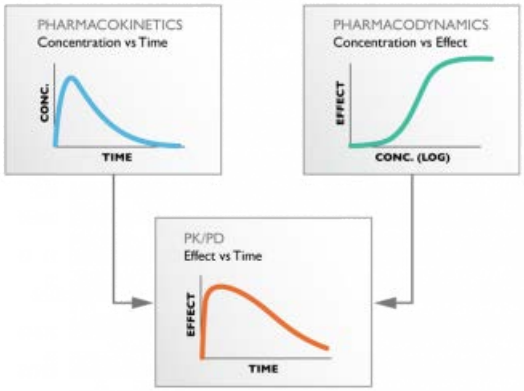


Release/ Absorption/ PBPK Models

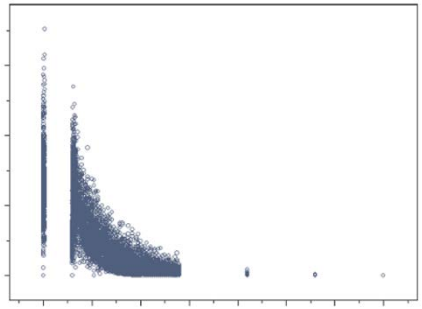
Big Data

Pharmaco metrics

Analytics for complex mixtures
Systems pharmacology
Risk models
Business process models



PK-PD model



Population model

Regulatory impacts

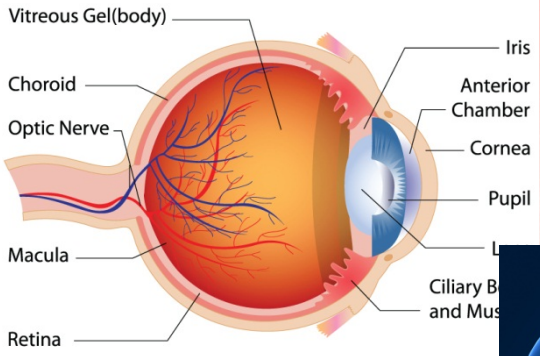
	Oral PBPK	Non-oral PBPK	PK/PD	Big Data	Systems pharmacology
Post-market Evaluation of Generic Drugs	√		√	√	√
Equivalence of Complex Products		√	√	√	
Equivalence of Locally Acting Products		√	√		
Therapeutic Equivalence Evaluation and Standards	√		√	√	√

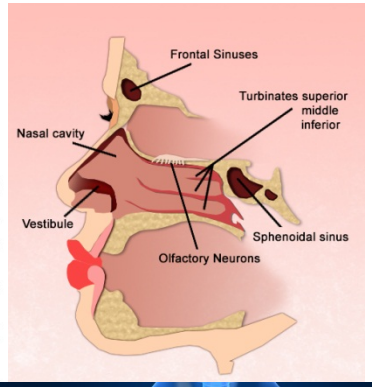
Physiologically based absorption and PK models

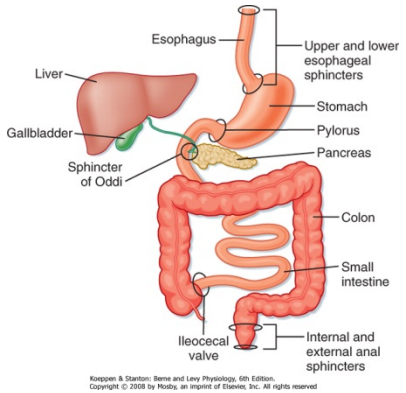
Drug substance
Formulations
In vitro performance

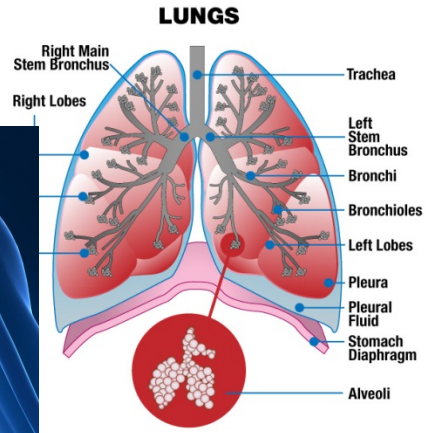
→ **Model** →

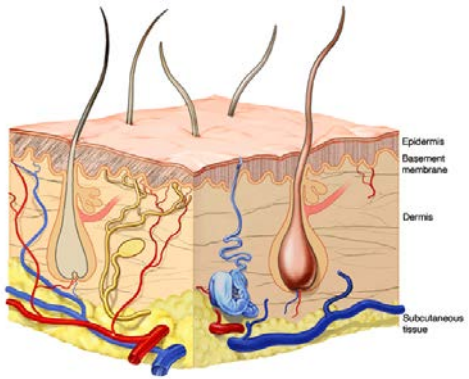
In vivo performance











Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

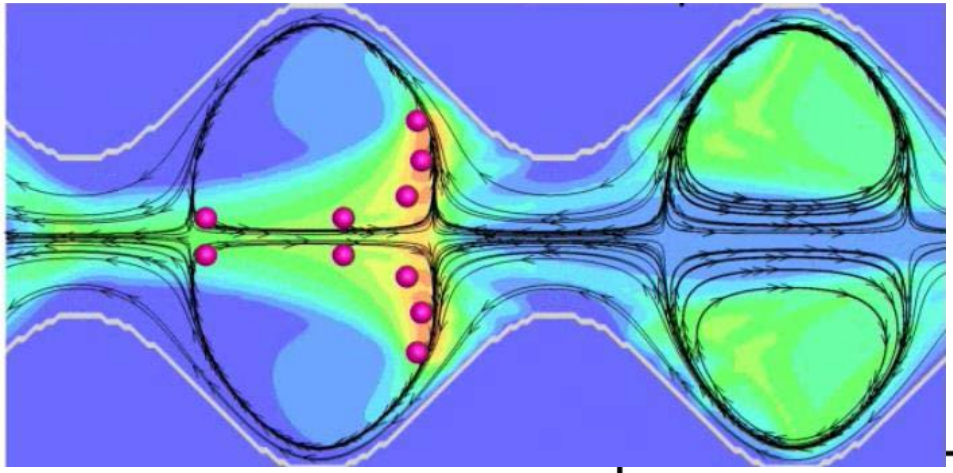
Knowledge Gaps

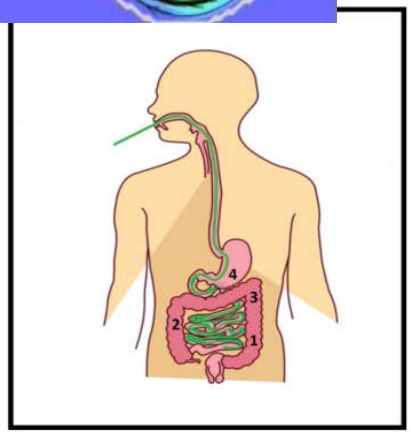
- Physiological identification of sources of within-subject variability
- Leveraging model complexity and model performance
- Model validation due to lack of actual data
  - Building confidence in reliability and performance of complicated mechanism based models
- Understanding physiology and pathology in sub populations, and drug effect on disease progression and its feedback on PK
- Developing in vivo relevant in vitro testing

Funded Studies

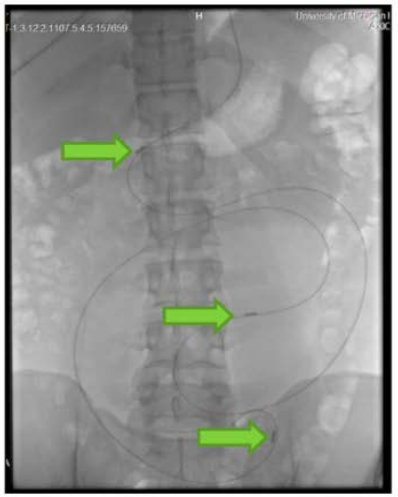
- GI absorption
  - Modernization of in vivo in vitro oral bioperformance prediction and assessment (University of Michigan)
- Topical and dermal absorption
  - University of South Australia, and Simcyp, LTD
- PBPK modeling for ocular dosage forms
  - Simulations Plus, Inc., and CFD Research Corporation
- Intranasal computational fluid dynamics (CFD)-PBPK modeling
  - Applied Research Associates, Inc.
- Lung CFD-PBPK absorption modeling
  - CFD Research Corporation
- PBPK modeling for complex parenteral injectables
  - State University of New York at Buffalo

Improve in vitro dissolution and oral absorption models





Port Locations:
1. Distal Jejunum/ Proximal Ileum
2. Proximal Jejunum
3. Duodenum
4. Stomach



Fluoroscopic photo of GI tube placement. Shown are 3 aspiration ports located in the stomach, proximal jejunum, and distal jejunum.

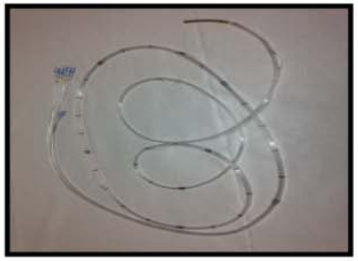


Photo of Multi-Lumen GI Tube

PK/PD & Pharmacometrics

- Best toolset to capture uncertainty
- Study simulations to assist BE study design
- Clinical trial simulations to assess sensitivity of PD endpoints
- PK-PD modeling to select the most appropriate PK metrics for BE assessment
- Exposure-response analysis to help define acceptance region for BE establishment
- Quantitative approach to define NTIs
- Basis to establish risk based standards

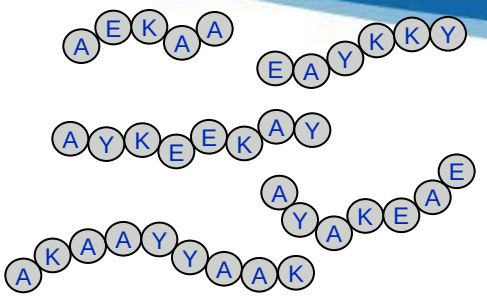
Knowledge Gaps

- Risk-based BE standards
  - What is the best BE metrics?
    - pAUC needed? Why? When?
    - Exposure-response relationship not well understood in NDA cycle to guide BE metrics selection
  - What is the best study design, i.e., long acting injectable products?
  - Equivalence of modified release solid oral dosage forms
    - Value of replicate design BE studies, pAUC and IVIVC
- Within-subject Variability
  - Important for crossover BE study simulations
  - Less understood compared to between-subject variability
- Mechanism-based approaches to evaluate generic substitution issues

Funded PK/PD Studies & Pharmacometric Grants

- Prospective PK/PD study with metoprolol ER products (University of Florida)
- Prospective PK/PD study with methylphenidate ER products (Massachusetts General Hospital)
- Pharmacometric grant on using population PK/PD approaches to classify NTI drugs (University of Maryland)
- Pharmacometric grant on evaluating pAUC as BE metric (University of Utah)
- System-based approach to evaluate generic substitution issues (University of Florida)
- Pharmacometric M&S to evaluate post-market risk (University of Maryland)

Big Data


AEKAA
EAYKKY
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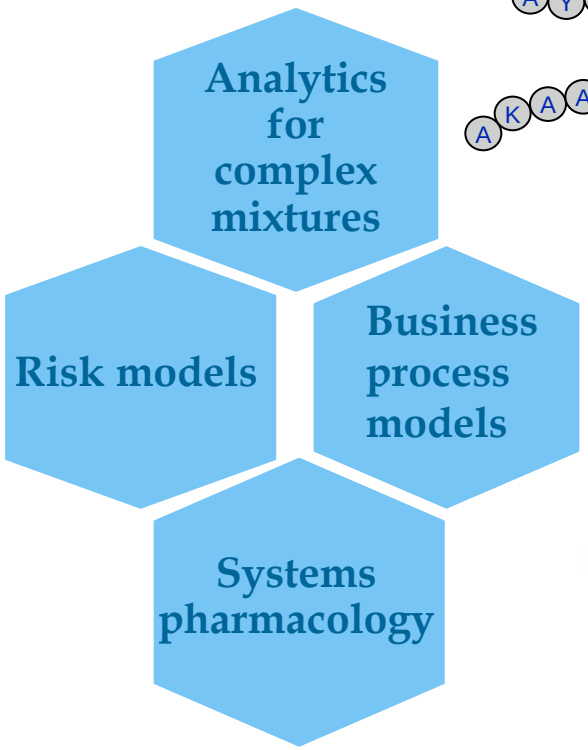
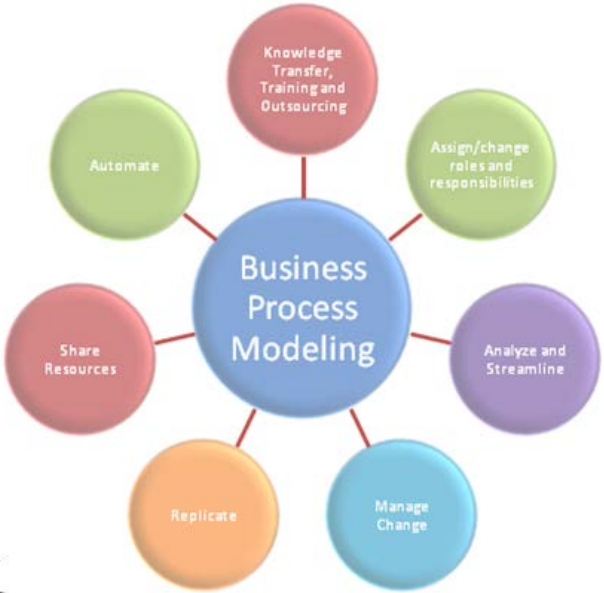
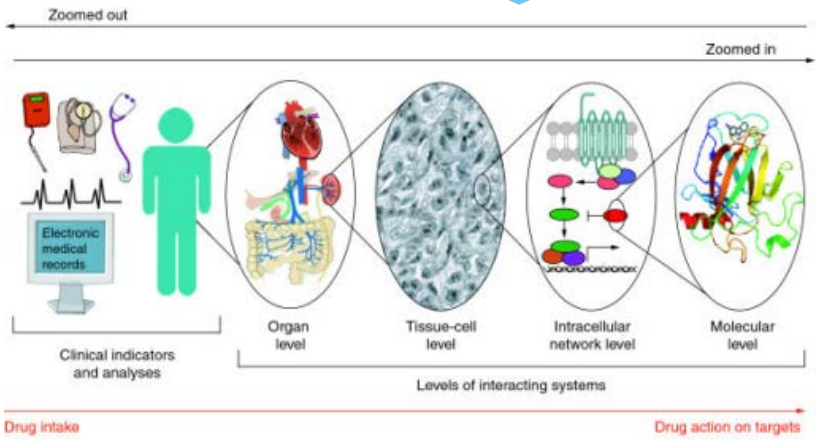
IDENTIFY
ANALYZE
RISK
MANAGEMENT
CONTROL
ACTION
MONITOR


Analytics for complex mixtures
Risk models
Business process models
Systems pharmacology

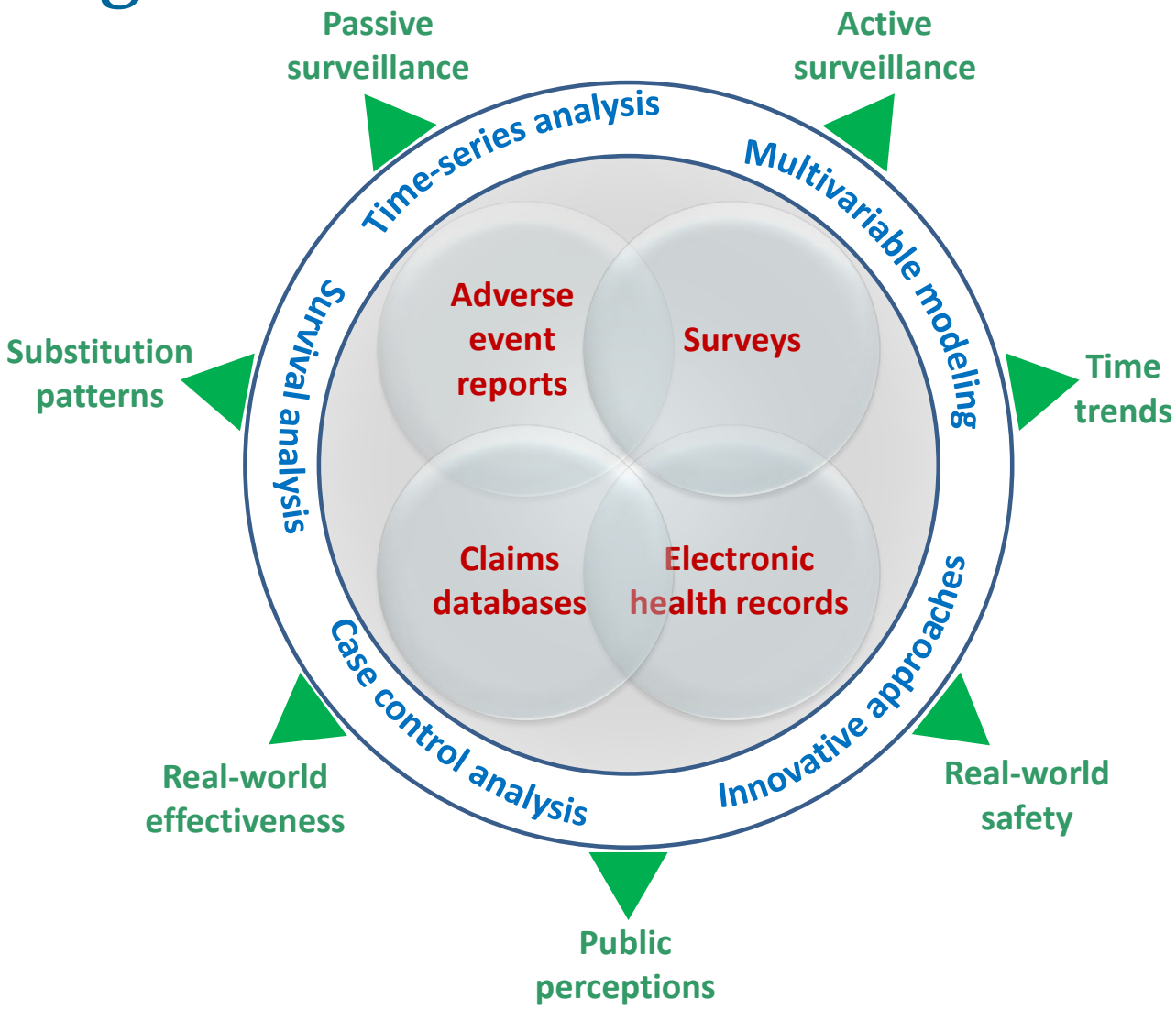

Knowledge Transfer, Training and Outsourcing
Automate
Assign/change roles and responsibilities
Business Process Modeling
Share Resources
Analyze and Streamline
Replicate
Manage Change


Zoomed out
Zoomed in
Electronic medical records
Clinical indicators and analyses
Organ level
Tissue-cell level
Intracellular network level
Molecular level
Levels of interacting systems
Drug intake
Drug action on targets

Tools for Complex Mixtures & Peptides

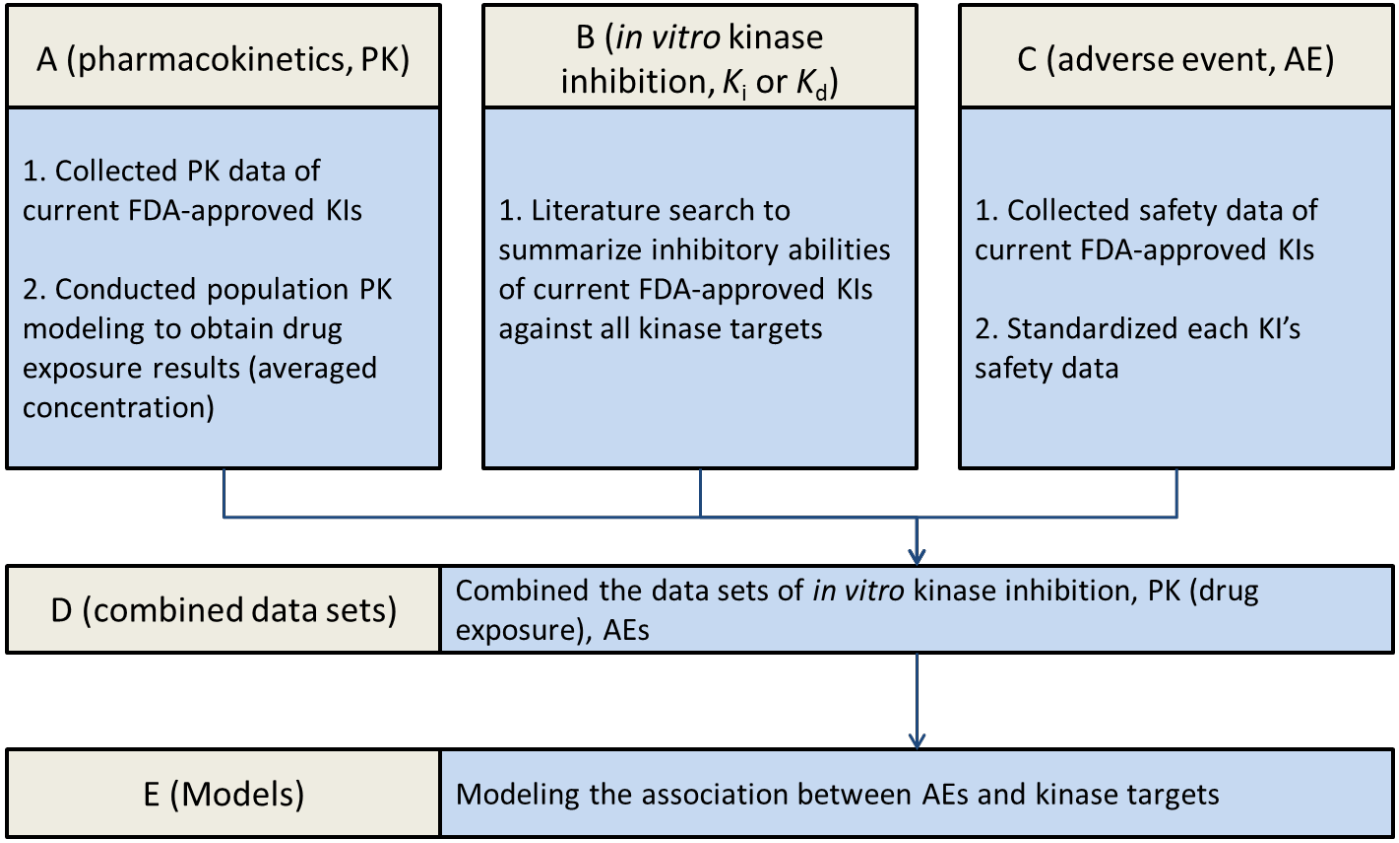
- Peptide-related impurity analysis using LC-HRMS
- Using in vitro assays to assess impurities on immunogenicity
- Using mathematical modeling to assess equivalence of complex mixtures based on physicochemical & biological characterizations

Quantitative approaches in the Post-Marketing Surveillance of Generics



Understanding safety risk

- Mechanism based: systems pharmacology
- Prediction based: association score & neural networks



A scheme for oncology AE by J. Liu

A Sample of Funded Safety Surveillance Grants

- Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns (Brigham & Women's Hospital)
- Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns (IMPAQ International)
- Variations in the Physical Characteristics of Generic Drug Pills and Patients' Perceptions: Surveys of Pharmacists and Patients (Brigham & Women's Hospital)
- Post-market Surveillance Evaluation of Authorized Generic Drug Products (Brigham & Women's Hospital)
- Post-market Surveillance Evaluation of Authorized Generic Drug Products (Auburn University)
- Effect of Therapeutic Class on Generic Drug Substitutions (Johns Hopkins University)

M&S Impact in OGD

Type	N	Examples
ANDA Reviews	6+	PD modeling and simulation for budesonide nasal spray to support the selected dose for BE study.
CP, CC, and Other Consult Response	53+	Development of BE criteria for zolpidem tartrate ER tablets Steady state simulations for risperidone long acting injection Simulation of in vivo alcohol dose dumping studies
BE Guidances	24+	Simulations for the development of BE criteria for complex drugs, HVDs and NTI drugs
Regulatory Research Study	7+	PK/PD modeling and simulation to determine the appropriate study design and evaluate BE between generic anti-epilepsy drugs and immunosuppressant drugs in patients.

Take Home Message

- For industry and consumer
  - M&S provide great value creation for generic developments and safety surveillance
- For the agencies:
  - M&S to be further engaged to inform guidance/policy development and regulatory decision makings
- For all stakeholders
  - M&S is an innovative and effective approach to make safe and effective generic drugs available to the American public

Source of figures in this slides

- Page 2
  - http://www2.lbl.gov/today/2007/Jul/11-Wed/7-11-07.html
  - http://www.carbodydesign.com/2010/11/new-level-mako-kit/
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  - The bottom figure adopted from Genome Med 1(1):11, 2009.
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